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Studies on the Respiratory Centre

I. THE BEHAVIOUR OF THE RESPIRATIONS AFTER DECEREBRATION IN THE CAT

By J. J. R. MACLEOD, M.B., F.R.S.C.

(Read May Meeting, 1919.)

Our knowledge of the functions of the respiratory centre depends on observations which have been made either on anæsthetised laboratory animals or on man in the normal state. To both groups of researches serious objections can be raised; to the former because of the use of anæsthesia, which is well known greatly to depress the excitability of the respiratory centre, and to the latter because of the limited variety of observations which it is practicable to make. As a first step to a further investigation of the respiratory function, therefore, it became necessary to seek for some method applicable to laboratory animals, in which the activities of the centre would not be dulled by the use of anæsthetics. It has been found that this requirement can be satisfactorily met by using the decerebrate preparation which was originally described by C. S. Sherrington,[1] and subsequently more closely studied by Theile,[2] Sherrington,[3] Forbes and Sherrington,[4] Miller and Sherrington[5], Weed[6] and Cobb, Bailey and Holtz[7].

The section of the brain stem is usually made about the level of the anterior corpora quadrigemina. After the effects of the initial anæsthesia have passed off a state of rigidity (plastic tonus) of the postural musculature supervenes and the breathing usually remains more or less normal.

In using the decerebrate preparation for investigation of the respiratory function one must not lose sight of the fact that important controlling influences have been removed from the centre, namely those derived from the higher cerebral centres, and that the respiratory function under these conditions may be as far removed from the normal as in an anæsthetised animal with brain intact. It is clear, however, that important facts are likely to be revealed by observing the behaviour of the decerebrated animal in relationship to changes in the chemical condition of the arterial blood, an investigation which is very difficult in man, and which can be carried out in anæsthetised animals only to a limited degree because of the presence of anæsthetics in the blood.

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[1] Sherrington, C. S. Journ. Physiol., 1897, XXII, 319.

[2] Theile, F. H. Journ. Physiol., 1904, XXXII, 358.

[3] Sherrington, C. S. Quart. Journ. Physiol., 1908, II, 109.

[4] Forbes, A, and Sherrington, C. S. Am. Journ. Physiol., 1915, XXXV, 327.

[5] Miller, F. R., and Sherrington, C. S. Quart. Journ. Physiol., 1915, IX, 147.

[6] Weed, L. H. Journ. Physiol., 1914, XLVIII, 205 and Am. Journ. Physiol., 1917, XLIII, 131.

[7] Cobb, S., Bailey, A. A., and Holtz, P. R. Am. Journ. Physiol., 1917, XLIV, 239.

It has been noted by several of the above-mentioned workers, particularly by Theile (loc. cit.) and Weed (Weed, L. H., Am. Journ. Physiol., 1917, XLIII, 131.) that the character of the respirations does not remain the same throughout the period during which the animal survives the decerebration. Weed recognizes three periods of somewhat different behaviour of the decerebrated animals; in the third of these, which supervenes in from two and one-half to three hours following the decerebration, increasing respiratory difficulties with rapid decline are often observed.

In a series of investigations, conducted in the author's laboratory by R. W. Scott, in which the particular problem was to study the influence of rapidly increasing percentages of carbon dioxide in the inspired air and of intravenous injections of alkali on the respiration of decerebrate cats (Scott, R. W., Am. Journ. Physiol., 1917, Vol. 44, 196), it was noted that there were three more or less distinct groups of animals. In one of these, adequate spontaneous respiration did not return, or if it did so it was irregular and incapable to maintain life. In a second group the breathing was fairly satisfactory for the first hour or so but then became dyspnoeic and gasping, and the animal soon succumbed. In the third group the animal breathed with perfect regularity for many hours, and even at the end did not develop the dyspnœa characteristic of the second group.

Since these variations might lead to serious confusion in the further researches which were contemplated, it was decided to make a closer study of the breathing and particularly to see whether variations in it are correlated with changes in the acid-base equilibrium of the blood. It is with this phase of the problem that the present paper is concerned.

METHODS

Decerebration was performed with the apparatus and by the method described by Miller and Sherrington (Quart. Journ. Physiol., 1915, IX, 107). It is of interest to note that frequently the respirations became regular almost immediately after the decerebration and remained so, particularly in young animals, even during compression of the vertebral arteries; whilst in other animals apnœa gradually supervened, but could be immediately terminated by allowing some arterial blood to reach the medulla by momentarily releasing the vertebrals. The reflex activities of the decerebrate animal varied considerably according to the exact position of the cut. When this was well forward of the anterior corpora quadrigemina the animals, after the effects of the anæsthetic had passed off, were highly excitable and behaved as if they felt some pain. Section by a scalpel a little further back immediately removed these mimetic reactions, but the resulting preparation was not as a rule so satisfactory as when the first cut had been in the correct position (*i.e.* through the anterior corpora quadrigemina). When the cut involved the posterior corpora quadrigemina spontaneous breathing rarely returned except in very young animals, and even in them it was usually irregular and unsatisfactory. In a succeeding paper we shall show that an abundant oxygen supply to the centre could usually be counted on to restore the breathing to normal in those cases in which it was irregular and spasmodic.

The alveolar air was collected by inserting into the trachea (through a side tube in the tracheal cannula) a narrow tube (gum-elastic catheter), the outer end of which was connected with an all-glass graduated syringe (10 cc., but capable of holding about 16 cc.) with the piston well smeared with vaseline. Towards the end of normal respiration the piston was withdrawn taking in from one half to one cubic centimetre. This process was repeated for several succeeding expirations after which the air was expelled again into the trachea so as to wash out the dead space of the tubing. By a repetition of the above procedure a sample of about 10 cc. of alveolar air was then collected for analysis. The analysis was carried out in a 10 cc. Haldane gas burette, the accuracy of which had been carefully checked against Brodie's apparatus.

There can be no doubt that the fractions of air collected towards the end of normal expirations is alveolar air in the usually accepted sense. The average tidal air of a cat is generally about 35 cc. and the dead space from the point of insertion of the catheter to the alveoli cannot be more than 10–12 cc. so that the last few cubic centimetres of air of a normal expiration, from which the fractions of 0·5–1 cc. are collected, must be undiluted alveolar air, even after allowing for the possibility that some of the peripheral layers of air in the trachea do not move so quickly as the axial currents (cf. Henderson, Chillingworth and Whitney, Am. Journ. Physiol., XXXVIII, p. 1).

Short of making actual comparisons of the tension of carbon dioxide in arterial blood and alveolar air, the most satisfactory evidence that the percentage composition of the alveolar samples collected by the present method really corresponds to the tension of the gas in arterial blood is supplied by the constancy of the results in successive samples of air. This constancy can be seen in the figures given in the tables accompanying this paper.

The percentage of carbon dioxide in the arterial blood was determined by the method of Barcroft and Haldane, using 0·5 cc. of blood and an excess of weak ammonia water, so that the precipitate which is formed when acid is added to dislodge the CO_2 does not make the solution so thick as to interfere with the evolution of the CO_2. The P_h of the arterial flow was measured by the method of Levy, Rowntree and Marriott (Archiv. of Int. Med., 1915, XVI, 389), the exact P_h of the phosphate solutions used for comparison being determined by the electro-metric method.

The total acidity of the urine was computed by adding (1) the titratable acidity (in cc. n/10 acid per 100 cc. urine), after shaking with excess of neutral potassium oxalate, using phenolphthalein as indicator, and (2) the ammonia, using the permutit method of Folin and Bell (J. Biol. Chem. N.Y., 1917, XXIX, 329).

The quantity of lactic acid in the blood was determined by the modified von Fürth method described elsewhere by the author (Macleod and Hoover, Am. Journ. Physiol., 1916–17, XLII, 460).

CONSIDERATION OF RESULTS

The present communication concerns the results obtained on cats which continued to breathe more or less normally for at least two hours following the decerebration. According to the behaviour of the breathing, as judged from the minute-volume of respired air, these animals could be divided into two main groups; in the one, the breathing either remained about constant or it slightly decreased, whilst in the other it progressively increased. In several animals of the first group the observation was terminated by bleeding to death, but in those of the second group it was usually continued until the animal died.

The results of a typical experiment of the first group of animals are given in Table I:

TABLE I

No. Expt.	Time after decerebration (min.)	Respirations per min.		Alveolar CO_2 %	Blood CO_2 %	Acid of Urine c.c.n/10 %	Rectal temperature	Remarks
		Vol. c.c.	rate					
XVIII	15	..	..	..	..	168	..	
	45	770	..	3·6	..	..	37·5	
	60	..	38	3·75	..	..	38	Rigidity moderate acoustic reflex and hyperexcitable.
	67	..	..	..	33	..	..	
	75	..	..	3·70	..	..	..	
	92	..	..	..	39·6	..	..	
	95	645	..	..	..	..	38·4	
	113	..	..	3·2	..	..	..	
	125	..	..	..	40·9	..	.	
	127	600	..	..	..	..	..	
	142	..	30	..	..	..	..	
	160	..	..	3·1	..	..	..	
	175	570	..	..	..	86	..	Glycosuria.
	200	..	..	3·0–3·5	..	..	37·3	After warming tank.
	225	616	..	..	38·2	..	..	
	238	..	33	..	..	..	38·5	
	257	..	..	3·2	..	..	..	Rigidity less.
	275	..	30	..	..	..	..	
	285	..	..	(3·6)	..	..	..	Rigidity almost gone.
	316	..	..	3·2	..	..	..	
	330	..	..	..	42·8	..	..	
	333	662	39	..	..	..		
	338	..	..	..	..	..	..	B.P. 70 mm. Hg.
						90 bled to	death	Glycosuria. P_h of blood at end 7·6

In more condensed form the results of the other observations of this group are given in Table II:

TABLE II

No Exp	Time after decerebration (min.)	Respirations per min.		Alveolar CO_2 %	Blood CO_2 %	Urine Acid c.c. N/10 %	NH_3 c.c.N/10 %	Remarks
		Vol. c.c.	rate					
VI	50-72	..	60	3·3	44·2	120	..	P_h of blood 7·4
	157-165	..	32	2·75	41	..	..	Decerebrate rigidity distinct.
	190-195	..	40	2·25	41	..	..	Temp. 39°C. P_h of blood 7·4. Bled to death
XIV	60-100	1100	..	3·5	52·8	..	..	Marked rigidity
♀	135-165	980	..	2·8	38·5	..	..	Rect. temp. 40°C.
	190-225	855	..	2·7	37	..	..	Rigidity pronounced.
	270-285	875	..	2·9	38·2	..	..	Rect. temp. 39°C.
	290-310	760	..	2·9	40·2	..	..	Lactic Acid 0·175%
XXVI	65-125	1000 -1040	40	4·5	..	..	..	Rect. temp. 39°C.
	155-215	825	32	4·1	..	28	..	Moderate rigidity
	230-240	845	34	4·4	..	..	..	Lactic acid 0·081%
	260-275	..	..	4·4	..	16	..	No glycosuria
XXIII	135-140	1080	27	3·3	..	106	0·107 0·076	
♀	195-215	1120 -1170	28	3·3	..	..	..	Rigidity slight
	230	1150	30	..	..	20	0·033	
	250-255	1120	28	3·0	..	..	..	
	290-295	940	25	2·9	..	..	..	P_h of blood 7·6–7·7
	302-305	960	22	..	45	6·5		Lactic acid 0·098% 0·101%
XII	45-60	..	64	3·6	40·2	..	..	Rigidity moderate
♀	110-115	..	42	3·9	39·6	..	38·5	

TABLE II—*continued*

No. Expt.	Time after decerebration (min.)	Respirations per min.		Alveolar CO_2 %	Blood CO_2 %	Urine Acid c.c. N/10 %	NH_3 c.c. N/10 %	Remarks
		Vol. c.c.	rate					
	135-147	..	36	3·9	..	..	..	Rigidity moderate
	217-247	..	..	3·1	41·0	..	..	
	265-285	..	..	2·4	37·0	..	..	
	305	412	42	2·0	38·0	..	39·5	B.P. very low
IX	60-79	217	..	4·3	40·8	..	..	Respiratory Quotient 0·68
	98-126	294	14	4·8	..	..	..	Rigidity marked
	131-146	394	16	4·5	44	..	..	Respiratory Quotient 0·74. Rigidity slight. Lactic acid 0·01 %

The following are considered the most noteworthy characteristics of these observations:

1. Both the respiratory volume and the respiratory rate decline gradually, although occasionally after four or five hours a slight increase may occur (cf. IX and XVIII). This increase is doubtless explained by the fact that the respiratory centre is hyperexcitable in decerebrate animals, so that the manipulation involved in withdrawing blood from the femoral artery for analysis, or in cleaning the femoral cannula of clots brings on a marked hyperpnœa which may last for some minutes after the irritation is removed.

2. The percentage of carbon dioxide in the alveolar air collected in from one to two hours after decerebration (when all ether has disappeared from the blood) varies between 3·3 and 3·9 in five of the six cats of this group, and in numerous observations which we have subsequently made this value has usually been found. Occasionally, and for no evident reason, the percentage may be somewhat higher as in experiments IX and XXVI. During the remainder of the period of observation the percentage of alveolar CO_2 either remains practically unchanged (XXVI) or it very gradually decreases.

In a series of decerebrate cats used in a research by Lois Fraser, R. S. Lang and the author, the alveolar air was analysed for both carbon dioxide and oxygen, and it is of importance in the present connection to place on record the respiratory quotients obtained in samples of air removed at varying periods over a time in which the animal was breathing normally. Table III gives these results. .

TABLE III

No. of Cat. (new series)	Time after decerebration (minutes)	Respiratory Quotient
X	100	0·71
	175	0·72
	210	0·71
XX	80	0·92
	115	0·90
	131	1·04
XXIII	70	0·72
	90	0·70
XXIV	60	0·89
	86	0·77
	172	0·81
	183	0·82
XXV	68	0·72
	83	0·71
	100	0·68
XXVI	126	0·81
	140	0·72
	161	0·85

It will be observed that, with two exceptions, the respiratory quotient varies in different animals from 0·7 to 0·9, indicating that a normal type of metabolism is in progress. The relative steadiness of the quotient in each animal further shows that the alveoli are being ventilated at a uniform rate.

3. The percentage of carbon dioxide in the arterial blood varies between 37 and 45 volumes per cent, with the exception of the first observations made on cats XVIII and XIV, in the former of which it is abnormally low and in the latter abnormally high. Both of these

exceptional results were obtained in blood removed in about one hour after decerebration, and subsequent experience has taught us that a longer period than this should have been allowed for the ether to have been expelled from the body. Throughout the remainder of the observations the carbonate of the arterial blood remains practically steady. It is impossible to say from the few results on hand and the small degree of fluctuation in the blood-carbonate values whether any parallelism exists between them and those of the aveolar CO_2.

4. Determination of the total acidity and ammonia content of the urine has not supplied results that can be satisfactory interpreted. In practically all cases, of this group as well as of others, in which sufficient urine was obtainable to estimate both the acidity and the ammonia content, a direct proportionality has been observed between the two, so that to follow changes in the acid excretion in a given cat either the titration or the ammonia values may be used. In the three experiments of this group in which there are adequate data a very decided decline in the acid concentration is observed, in fact in two of the animals, XXVI and XXIII, the urine became nearly neutral. Whether this result depends upon a failure of the kidney to remove acid radicles from the blood or upon a relative increase in fixed alkali in the organism cannot be said.

5. The hydrogen-ion concentration of the arterial blood remained normal, at P_h 7·4, in one of the animals, but it became less, *i.e.* P_h became greater (7·6–7·7) in two of them (XVIII and XXIII). On account of technical difficulties it was impossible to secure sufficient data to make certain that these changes are real, but further observations will be published shortly. If a real increase in P_h does occur it would indicate that the decreasing acidity of the urine, above referred to, is dependent upon alkali retention.

6. Lactic acid was determined in the arterial blood of three of the experiments. In two of them (XXVI and XXIII) it varied between 0·081 and 0·101 per cent. In the third (XIV) it was much higher, namely, 0·175 per cent. It is important to note that the last estimation is possibly too high because the extraction with ether had to be performed in two portions of the unevaporated protein-free filtrate. This would relatively increase the error due to any impurities in the reagents.

It is of interest in this connection to place on record results obtained for lactic acid in the blood of two cats which were bled solely for this purpose immediately after anæsthetising with ether. These are as follows: 0·052 per cent (Cat No. XXVIII) and 0·113 per cent (Cat No. XXIX). It is clear that considerable variation exists in the lactic acid content of cat's blood even under approximately normal conditions. Partial asphyxiation, due to the ether, may explain the variability.

7. Other occasional observations included testing the urine for sugar, the extent of muscular rigidity, and the arterial blood pressure. Glycosuria, when tested for, did not appear so frequently in the cats of this group as in those of the second group. On account of difficulties with clotting, to which the blood of many decerebrate animals appears to be very prone, and because of lack of assistance, it was impracticable to secure many records of arterial blood pressure. In about five hours after decerebration in Cat No. XVIII, however, it was 70 mm. Hg., and from the ease with which the blood flowed from the femoral artery for the lactic acid estimation, it must have been at this height, at least, in the case of the other experiments.

The degree of decerebrate rigidity varied considerably in the different preparations.

A typical observation of the group of animals in which hyperpnœa developed is given in Table IV:

In all of the animals of this group the decerebration was performed well forward of the anterior corpora quadrigemina and the decerebrated animal was very excitable, hyperpnœa being induced by the slightest disturbance. As a rule this hyperpnœa was transient (cf. Exp. XXII) and in all the animals the respirations progressively increased in volume and rate without any evident afferent stimulation. In the most extreme cases (Nos. X, XXX and XXXI) death occurred in about two hours after decerebration, being usually preceded by vomiting movements and convulsions. The rapid development of these conditions made it impossible to analyse many samples of alveolar air or blood for CO_2, so that attention was rather given to securing samples of blood and urine of adequate size so that lactic acid, H-ion concentration and the acid excretion might be ascertained. The following observations are noteworthy:

1. If we take the average minute volume of respired air of a normal decerebrate cat as 1000 cc. (cf. R. W. Scott, Am. Journ. Physiol., 1917, XLIII, p. 169), it is seen that in about one hour after decerebration all the animals of this group were respiring normally, although usually somewhat rapidly, the average for normal animals being 20–25 per minute. The hyperpnœa which subsequently developed either did so gradually (Nos. XVII and XXII) or, after doing so for a time, suddenly became much more pronounced (XXX and XXXI), this type being especially prominent in hyperexcitable preparations.

TABLE IV

No.	Time after decerebration. min.	Respirations. cc. per min.	Alveolar CO_2 %	Blood CO_2 %	Urine n/10 acid %	n/10 NH_3 %	Rectal Temp.	Remarks
XVII	..	..	..	..	82	..	..	Cut far forward. Perhaps slight asphyxia
	25	..	..	..	..	..	..	
	45	..	5·0	..	..	..	..	B.P. 120 mm. Hg.
	55	..	4·9	..	..	..	39	
	60	..	..	41·6	..	..	..	Rigidity slight
	75	916	..	..	..	..	39·8	B.P. 110 mm. Hg.
	80	..	4·5	43·6	..	..	..	
	95	1020	..	..	88	0·16	..	Glycosuria
	105	..	..	..	..	..	..	Occasional sighs
	115	..	3·4	..	..	..	39·8	
	121	1130	3·1	..	..	..	..	
	134	1180	..	..	..	..	..	
	150	..	2·8	..	..	..	..	
	155	..	1·8	..	..	..	..	
	160	..	1·8	..	..	..	..	B.P. 55–60 mm. Hg.
	166	1430	..	31	..	..	..	Rigidity slight
	173	..	2·0	..	..	..	..	
	176	1430	1·9	..	..	..	..	
	191	1720	..	29	..	..	..	
	205	..	1·6	..	..	..	..	
	209	1500	..	27·7	..	..	..	
	215	1560	..	..	..	..	..	Very rigid.
	235	..	..	..	28	0·04	..	Glycosuria. Lactic acid 0·121 % P_h not done

The abridged results on other animals that showed the same behaviour are given in Table V:

TABLE V

No.	Time after decerebration min.	Respirations per minute		Aveolar air CO_2 %	Blood CO_2 %	Blood Ph	Urine		Rect. Temp.	Remarks
		cc.	rate				n/10 %	n/10 %		
X	71			3·6						Cut far forward
	93	850	30		20·4					Animal hyper-excitable and dyspnoeic from start, rigidity marked.
	108		..		..	7·1				Moribund when Ph measured.
XXII	53	1125	..	3·5	.		.		39	Cut well forward.
	70									
♀	73 93	1085	28	3·6	..		30		39	
	108–118	1225	..	3·3	..	..			40	Animal became suddenly hyperpnoeic.
	133		38	2·9	..	7·4				Rigidity marked.
	–148									
	178	..	44	1·9	..	..			40	Vomited.
	203–208	..	..	1·7	24·4	7·1	30			Lactic Acid 0·296 %. Very slight glycosuria.
XXX	74	1290	26	.	..		56·6	0·168	39·5	Cut well forward.
♀	100	1660	28	..	..	.	.			Rigidity marked.
										Hyperexcitable.
	125	2750	40	.	..	7·0 7·1	93·0			
								0·142	40·5	B.P. 70 mm. Hg. at end.
XXXI	62	1120	36	..	..			.	38	Cut well forward.
♀	113	2100	48	.	.					Rigidity marked.
	142	3200	64		.		..		38·5	Hyperexcitable.
	146	3930	69			7·0 7·1			38·5	Lactic acid 0·232 %. B.P. below 40 mm at end

2. The alveolar air was analysed for CO_2 in two of the cats and it shows a progressive decrease which was more or less in proportion to the increase in ventilation. There is only one experiment in which sufficiently numerous data were secured to determine the precise relationship between rate of increase in ventilation and alveolar CO_2. In this experiment an increase in volume from 916 to 1130 cc. per minute corresponds to a fall in percentage of alveolar CO_2 from 4·5 to 3·1, giving 1·4 per cent increase in CO_2 for 214 cc. increase in air breathed. Later, an increase in ventilation from 1180 to 1720 cc. per minute corresponds to a decrease in CO_2 percentage from 2·8 to 1·6 giving 1·2 per cent decrease in CO_2 for 540 cc. increase in air breathed. These results indicate that the ventilation increases out of proportion to the decrease in alveolar CO_2.

3. The carbonate content of the blood decreases markedly in all the three cases (X, XVII and XXII) in which it was measured, but there are not sufficient data to say whether this is dependent upon a "blowing off" of CO_2 through the lungs, an "acapnia" in Mosso's sense, or is due to the appearance of fixed acids in the blood. It has been observed by Cannon and others[1] working on the problem of surgical shock that the CO_2 absorbing power of the venous blood invariably becomes lowered when there is a decided fall in the arterial blood pressure. In a general way a similar relationship appears to exist in our observations, but it is impossible to conclude from the data available whether the two values bear any necessary relationship to each other.

4. The H-ion concentration of the arterial blood, measured in four of the observations, before *exitus* becomes decidedly raised (P_h 7·0–7·1). In two of the experiments (Nos. X and XXXI) the animal was practically dead when the blood was collected, so that the low P_h may not be of much significance. In the case of the other two experiments (Nos. XXX and XXII), however, the specimens were collected while the animal was still breathing and they indicate a very decisive degree of acidosis.

5. Lactic acid was measured in three of the animals and is found to be markedly increased in two (XXII and XXXI) and about the upper limit of the normal value in the third (XVII). This observation corresponds with those made on P_h and would indicate that the primary cause for the lowering of the blood carbonates and for the hypernœa is the development of unoxidised acid in the organism.

6. The acid excretion by the urine is depressed in the least acute of the experiments (XVII) in which also there is no decided increase

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[1] Cannon, W.B., Journ. of the Amer. Med. Assn., 1918.

in the lactic acid content of the blood, but it remains constant or increases in two experiments in which the hyperpnœa developed acutely (Nos. XXII and XXX) and an excess of lactic acid and a marked lowering in P_h of the arterial blood is evident. Inasmuch as the acid excretion in all of the normal decerebrate animals becomes markedly depressed, it is significant that in those animals of the hyperpnœa group the acid excretion should have continued high.

7. Decerebrate rigidity was very marked in the four animals of this series in which there was excessive hyperpnœa and was slight in that (XVII) in which this was of lesser degree. This observation is possibly of interest, since it suggests that the accumulation of lactic acid, which was very high in two of these cases, may depend on the abnormally contracted musculature. According to such a view, in the state of permanent (plastic) tonus the blood supply to the muscles may be inadequate to supply sufficient oxygen to effect the oxidative removal of the lactic acid which therefore accumulates and overflows into the blood. With regard to the rectal temperature it will be noted that this usually rose somewhat, but not sufficiently to account for the dyspnœa.

Glycosuria of slight degree was observed in two of the experiments; sugar was not examined for in the urine of the other animals.

It may appear that the division of the animals into two groups, according to whether or not decided hyperpnœa became established, is arbitrary and that certain of the observations should have been classified as belonging to an intermediate group. Although this is true, it is nevertheless, we believe, more correct to adopt the present classification since it corresponds to the general impression, which is conveyed by actual experience with decerebrate animals. As a matter of fact, the above records include, out of a total of twenty animals, all those save one in which satisfactory spontaneous regular breathing existed one hour after the decerebration. In the one exception, the breathing was excessively rapid and deep, the aveolar CO_2 well below two per cent and the blood carbonate below twenty per cent. Although the rigidity was of slight degree this animal was extremely hyperexcitable, the section being well forward of the anterior corpora quadrigemina, and the hyperpnœa was definitely dependent upon afferent stimulation induced by faulty technique in catheterization.

In seven of the twenty animals satisfactory breathing did not spontaneously return within one hour after the decerebration, and the animals were discarded. It was usually the case that the section in their cases was well back, but its exact position has not been recorded.

We have preserved the anterior portions of the heads of numerous animals in subsequent experiments of a similar type, and we hope in the near future to be able to furnish data which will enable us to state precisely where the cut should be situated for satisfactory breathing. As far as we can say at present when the posterior corpora quadrigemina are even slightly wounded spontaneous respiration is seldom, if ever, observed.

In collaboration with Lois Fraser and R. S. Lang, I have found, however, that perfectly regular respirations may reappear in animals of the above type by greatly raising the partial pressure of oxygen in the alveolar air. This is done by passing a catheter into the trachea so that its open end lies above the bifurcation, and then discharging washed oxygen at a rapid rate from a cylinder of the gas. In a few minutes, during which artificial respiration may be necessary in order to carry the oxygen to the alveoli, the animal usually begins to breathe in perfectly normal fashion and continues doing so for hours. We are at present engaged in studying the very interesting and far-reaching problems which this observation presents; for the present we may point to the interesting evidence it affords that oxygen deficiency, *per se*, far from acting as a stimulus for the respiratory centre, renders it incapable of rhythmic function, at least in conditions where it is imperfectly supplied with blood, as after decerebration. In this connection attention should again be called to the fact that if the breathing of the decerebrate animal becomes feeble during compression of the vertebral arteries, it can be restored to normal by releasing the blood flow.

CONCLUSIONS

After removal of the cerebral hemispheres a certain number of cats continue to breathe in perfectly normal fashion for several hours; others fail to respire adequately and still others breathe normally for some time, but subsequently become hyperpnœic, and finally are usually seized by convulsions to which they succumb. These differences in behaviour seem to be dependent upon the age of the animal and the level at which the section of the mesencephalon is made. Spontaneous breathing is decidedly more likely to return in the younger animals and when the cut is not further back than the anterior edge of the anterior corpora quadrigemina. When the cut is further forward the decerebrate animal is hyperexcitable, decerebrate rigidity is marked, and the animal usually becomes hyperpnœic. When the cut is farther back, adequate spontaneous breathing is unusual.

Particular attention is given in the present research to the possible cause of the hyperpnœa. With this object in view the behaviour of the percentage of carbon dioxide in the alveolar air and arterial blood as well as the hydrogen-ion concentration and the percentage of lactic acid in the latter have been compared with the respiratory behaviour of the animal. The acid excretion by way of the urine has also been observed.

It has been found that the above-mentioned values remain tolerably constant in the animals which do not become hyperpnœic but that in those which do so the alveolar-CO_2 steadily declines, accompanied or followed by a decline in blood carbonates and by a decided increase in the hydrogen-ion concentration and lactic acid content of the arterial blood. These blood changes indicate that unoxidized acid, lactic, has accumulated in the blood and the main question to be considered is whether the hyperpnœa is the result of the accumulation of acid or whether the acid accumulates because of hyperpnœa. Concerning the first hypothesis the close attention which has been given in recent years to the condition known as acidosis has shown that there are three characteristic signs of the condition: first, a decrease in the percentage of carbon dioxide in the alveolar air; secondly, a decrease in the ability of the blood to combine with this gas, and thirdly, an increased excretion of free acid by the kidney. Now it will be noted that the first two of these characteristics are very prominently affected in those decerebrate cats which became hyperpnœic, and that the third, acid excretion in the urine—in the cases in which it could be measured, remained decidedly higher in the hyperpnœic animals than in those that breathed normally. If we add to these indirect evidences of an acidosis condition the further evidence afforded by a determination of the hydrogen-ion concentration of the arterial blood there seems little doubt that an intoxication by acid must have been the cause of the hyperpnœa. As to the nature and source of this acid there is evidence that it was lactic acid—large percentages being found in the arterial blood—which may have been derived from the plastic tonus of the muscles of the decerebrate animals, for this condition, though present in all the animals, was especially prominent in those that became hyperpnœic. It has been shown by Roaf (Quart. Journ. Exp. Physiol., 912, V, 31-53) that the gaseous metabolism of decerebrate cats is no greater than that of animals whose muscles are paralysed by curare, which indicates that very little energy can be expended notwithstanding the permanently contracted state of the muscles.

If we accept the modern view which is the outcome of the work of F. Gowland Hopkins and Fletcher (Proc. Roy. Soc. Lond., 1917, Ser

B, LXXXIX, 444) that the lactic acid which is produced by a muscular contraction is removed by an oxidative process before the next contraction takes place, then it is conceivable that in the permanent contraction, to which plastic tonus corresponds, the acid fails to disappear from the muscle so that it overflows into the blood, in which it accumulates, since it can no longer be removed by oxidation, and from which it is only gradually excreted.

In brief, then, the simplest interpretation for the hyperpnœa and final collapse of many decerebrate animals is that it is caused by acute acidosis brought about by an accumulation of lactic acid derived from the permanently contracted extensor musculature which is characteristic of this condition. But we do not intend to imply that this hypothesis is proven by the observations of the present research. In so far as the results themselves are concerned there can be no doubt as to the reliability and tolerable accuracy of the values given for the carbon dioxide of the alveolar air and blood, but there is a possibility of error in connection with those for the P_h and lactic acid content of blood. The greatest care has been taken in the analyses and they have always been carried out under strictly standardized conditions, but nevertheless it is possible that the samples of blood on which they were carried out were removed when the animal was already in a moribund condition, in which because of failing circulation such changes as were observed are to be expected. To circumvent this possible source of error blood was taken from one of the hyperpnœic animals (Table IV, No. XXX) while the arterial blood pressure was still above 70 mm. Hg., with the same results. Further observations of a similar type are, however, necessary.

With regard to the second hypothesis, namely that the organic acid of the blood rises to take the place of the carbonic acid which is blown off because of hyperpnœa induced by afferent stumuli acting on a hyperexcitable respiratory centre, little that is definite can be said. In support of this view, however, stands the fact that the animals exhibiting the hyperpnœa were invariably those in which, because of the forward position of the section, there was decided hyperexcitability of the nerve centres.

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